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Early and Long-Term Outcomes After Combined Percutaneous Revascularization in Patients With Carotid and Coronary Artery Stenoses

Fabrizio Tomai, MD,* Gabriele Pesarini, MD,† Fausto Castriota, MD,‡
Bernhard Reimers, MD,§ Leonardo De Luca, MD, PHD,* Giovanni De Persio, MD,*
Daniela Spartà, MD,† Cristina Aurigemma, MD,* Andrea Pacchioni, MD,§
Barbara Spagnolo, MD,‡ Alberto Cremonesi, MD,‡ Flavio Ribichini, MD,†
for the FRIENDS (Finalized Research in Endovascular Strategies) Study Group

Rome, Verona, Cotignola, and Mirano, Italy

Objectives This study sought to evaluate the 30-day and long-term clinical outcomes of patients with carotid obstructive disease (COD) and concomitant coronary artery disease (CAD) undergoing a combined percutaneous revascularization, in 4 high-volume centers skilled for the treatment of multilevel vascular disease.

Background The optimal management of patients with COD and concomitant CAD remains controversial. A variety of therapeutic strategies, including coronary artery bypass grafting, alone or in combination with carotid artery revascularization, have been reported.

Methods Between January 2006 and April 2010, 239 consecutive patients with COD (symptomatic carotid stenosis in 20.5%) and concomitant CAD were treated with staged or simultaneous carotid artery stenting and percutaneous coronary intervention, and enrolled in this prospective registry. The primary endpoint was the incidence of major cardiac and cerebrovascular events, including any death, myocardial infarction, or stroke occurring between the first revascularization procedure and 30 days after treatment of the second vascular territory affected.

Results The incidence of the primary endpoint at 30 days was 4.2% (95% confidence interval [CI]: 2.02 to 7.56). The rate of death, myocardial infarction, and stroke at long-term follow-up (median 520 days) was 4.2%, 2.1%, and 3.8%, respectively. At long-term follow-up, patients with previous cardiovascular disease had significantly higher rates of major cardiac and cerebrovascular events than did patients with a first clinical episode (17% vs. 6%, hazard ratio: 3.34; 95% CI: 1.46 to 7.63; $p = 0.004$).

Conclusions In patients with COD and concomitant CAD, a combined percutaneous treatment compares favorably with previous surgical or hybrid experiences. Such strategy may be particularly suited to complex patients at high surgical risk. (J Am Coll Cardiol Intv 2011;4:560–8) © 2011 by the American College of Cardiology Foundation

From the *Department of Cardiovascular Sciences, European Hospital, Rome, Italy; †Department of Medicine, University of Verona, Verona, Italy; ‡Gruppo Villa Maria (GVM) Care and Research Cardiovascular Unit, Villa Maria Cecilia Hospital, Cotignola, Italy; and the §Division of Cardiology, Ospedale Civile, Mirano, Italy. The authors have reported that they have no relationships to disclose.

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The coexistence of atherosclerosis in the coronary and carotid districts is a pathological condition that continues to expand in parallel with life expectancy (1,2). However, in the absence of randomized trials, the optimal treatment of patients with severe carotid obstructive disease (COD) and concomitant coronary artery disease (CAD) is not well established (3,4). A variety of therapeutic strategies, including coronary artery bypass graft (CABG), alone or associated with staged or simultaneous carotid endarterectomy (CEA) (5) or carotid artery stenting (CAS) (6), have been reported in different patient groups. Nevertheless, the incidence of death, stroke, or myocardial infarction (MI) with such strategies is high and varies from 7% to 14% (3–6).

Although a direct comparison of percutaneous to surgical coronary and/or carotid artery revascularization may not be valid in patients with CAD and concomitant COD, as these procedures are likely to be performed in different patient groups based on anatomical and clinical features, CAS and percutaneous coronary intervention (PCI) have recently proved to be accepted alternatives to CEA and CABG in high surgical risk patients (7–11). Indeed, CAS has been shown to course with less MI despite a statistically significant increment of stroke when compared with CEA (9), supporting the concept that CAS may be safer in patients with atherosclerosis extended to the coronary district. By contrast, PCI has been demonstrated to be at least equivalent to CABG in terms of death, stroke, or MI (10), and it is particularly suited in patients with unstable clinical presentation or with multiple comorbidities that increase the intraoperative surgical risk (11). Furthermore, the presence of COD is associated with a significant increase in death and stroke in patients undergoing CABG (12,13).

Because it has the least invasive nature, a combined percutaneous revascularization in patients with significant COD and CAD might be particularly appropriate for such a complex subset of patients at high surgical risk. Thus, the aim of this study was to evaluate the early and long-term outcomes of a combined percutaneous revascularization strategy in a population of patients with COD and concomitant CAD, treated by CAS and PCI, in 4 high-volume centers skilled for the treatment of multilevel vascular disease, which comprise the FRIENDS (Finalized Research in Endovascular Strategies) Study Group (14).

Methods

FRIENDS is a spontaneously generated, independent, not-for-profit working group. Present members are engaged at high-volume Italian institutions, committed to cardiovascular care, and work with a shared intention under common coordination (14). The FRIENDS study is the first large, multicenter registry including 659 patients with combined COD and CAD undergoing percutaneous, hybrid, or surgical revascularization treatments. The 30-day results of the overall population have been reported previously (15). This report presents the short- and long-term outcomes in the pre-specified subgroup of patients (n = 239) undergoing a combined percutaneous revascularization.

Patient population. In this prospective, multicenter, nonrandomized study, we enrolled consecutive patients scheduled for carotid and coronary angiography on the basis of clinical symptoms, noninvasive diagnostic tests for myocardial ischemia, and carotid Doppler ultrasound findings, and who were suitable candidates for CAS and PCI in each participating center. Patients were extracted from the common FRIENDS database, which was designed to abridge individual datasets collected in each center. All patients included in this study gave informed consent to undergo the proposed treatment and follow the pre-specified follow-up program. The ethical committees of each participating institution were informed about the aims and methods of this study.

Each of the participating centers developed a local team of experts in vascular medicine to jointly evaluate the therapeutic indications in this specific patient setting (14). The cardiovascular team included cardiac and vascular surgeons, clinical and interventional cardiologists, and neurologists. To be enrolled into the study, patients had to be considered suitable for PCI and CAS by the cardiovascular team after diagnostic coronary and cervical-cerebral angiography performed according to standard techniques. Patients were considered eligible for PCI if they presented documented myocardial ischemia and at least a significant angiographic stenosis ≥70% in 1 of the major coronary branches. According to clinical presentation, CAD was classified as stable (including patients with silent ischemia) or acute coronary syndromes (ACS), including patients with unstable angina, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. Neurologically asymptomatic and symptomatic patients were considered eligible for CAS if they presented a stenosis involving the internal carotid artery at selective angiography of ≥70% or ≥50%, respectively. Patients were considered neurologically symptomatic if an ipsilateral cerebrovascular event (including transient ischemic attack, amaurosis fugax, ischemic stroke, or retinal infarction) had occurred within the prior 6 months.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

CABG = coronary artery bypass graft

CAD = coronary artery disease

CAS = carotid artery stenting

CEA = carotid endarterectomy

CI = confidence interval

COD = carotid obstructive disease

MACCE = major cardiac and cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TIA = transient ischemic attack(s)

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Percutaneous revascularization strategy and technique. Simultaneous interventions were considered as those performed during the same access to the catheterization laboratory, or within the same day. In cases of very complex vascular access or concomitant acute severe carotid and coronary syndromes, CAS was combined with PCI during the same procedure (16). Staged interventions were intended as those performed within a range of 1 to 45 days from the first procedure. The sequence of interventions was established on an individual patient basis by the cardiovascular team, usually according to clinical symptoms of the patients and after diagnostic coronary and cervical-cerebral angiography. The first percutaneous procedure was performed on the priority vascular district immediately after the diagnostic angiography and during the same access.

According to standard clinical practice, PCI was performed via a 6- or 7-F sheath in the femoral or radial artery. Procedural success was defined as an angiographic residual diameter stenosis <20% by visual estimation, without the occurrence of cardiac death, Q-wave or non–Q-wave MI, or repeat revascularization of the target lesion during the hospital stay. In patients with multivessel CAD, the most complete degree of revascularization was attempted, unless contraindicated by severe comorbidities or particularly unfavorable anatomy.

The CAS procedures were performed via a 7-, 8-, or 9-F sheath in the femoral artery by positioning a guiding catheter in the common carotid artery, proximally to the bifurcation. If this was not possible due to the particular anatomy of supra-aortic vessels, a stiff wire was placed into the external carotid artery, for positioning of a long sheath or a guiding catheter (coaxial technique) into the common carotid artery. Cerebral protection with filter wires or with proximal occlusion devices was used in all patients. Different types of self-expandable stents were used according to individual clinical and anatomical characteristics as recommended by experts (17). After stent deployment and atropine administration, stents were post-dilated with a balloon (5.0 to 7.0 mm) to achieve a residual stenosis ≤30%.

Pre-procedural antithrombotic therapy consisted of aspirin and heparin at standard dosages and clopidogrel at a loading dose of 300 mg. In case of staged procedures, aspirin and clopidogrel were not discontinued between the first and second interventions. After the percutaneous procedure, dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was maintained for 1 month in all patients and was extended to 12 months after drug-eluting stent implantation and in all patients presenting with ACS regardless of the type of coronary stent. Aspirin alone was advised indefinitely in all cases.

Study endpoints. The primary endpoint of the study was the incidence of major cardiac and cerebrovascular events (MACCE), including any death, MI, or stroke occurring between the first revascularization procedure and 30 days after treatment of the second vascular territory affected.

Secondary endpoints were the cumulative incidence of MACCE, transient ischemic attacks (TIA), major bleeding, acute kidney injury at 30 days after both procedures, and the incidence of MACCE at long-term follow-up.

Endpoint definitions. Deaths were considered irrespective of their etiology. Fatal stroke (ischemic or hemorrhagic) and fatal MI were defined as deaths. Nonfatal MI included periprocedural MI (diagnosed by a rise in creatine kinase-myocardial band fraction of 3× the upper limit of normal), reinfarction (defined as recurrence of symptoms together with ST-segment elevation or new left bundle branch block and an increase in cardiac enzymes after stable or decreasing values), or spontaneous MI (diagnosed by any rise in creatine kinase-myocardial band fraction above the upper limit of normal). Electrocardiograms and cardiac enzymes were assessed routinely after both PCI and CAS procedures.

Stroke was defined as an acute ischemic neurological event that persisted ≥24 h, as assessed by a neurologist and confirmed by brain imaging. Strokes were considered disabling (major) if patients had a modified Rankin score of >3 at 30 days after onset of symptoms. A minor stroke was defined as a Rankin score of 3 or less that resolved completely within 30 days. Amaurosis fugax and TIAs were diagnosed if the symptoms disappeared within 24 h. The neurological status was assessed by a neurologist before and after CAS procedures in all cases.

Acute kidney injury was intended as a rise in serum creatinine of >0.5 mg/dl or a 25% increase from the baseline value, assessed at 72 h after CAS and PCI (18). Major bleeding was defined according to recent interventional trials (19).

Data collection and patient follow-up. Patients' data were entered in a common dedicated database. Clinical follow-up was obtained prospectively by either clinical visits or telephonic contacts at 30 days after both procedures and thereafter at 6-month intervals.

Statistical analysis. Continuous data are expressed as mean ± SD or median (interquartile range), where appropriate; discrete variables are given as absolute values and percentages. Univariate analysis to test the relation between the clinical and treatment variables and the occurrence of events included in primary and secondary endpoints were performed by means of binary logistic regression, obtaining also the odds ratio for each parameter. The association between clinical and treatment variables and MACCE at 2-year follow-up was assessed by means of a Cox proportional hazards regression analysis.

Kaplan-Meier survival tables and plots were also provided. A probability value of <0.05 for 2-sided statistics was considered significant. SPSS (version 15, IBM Corporation, Somers, New York) and Excel (Microsoft, Redmond, Washington) were used for data analysis.

Results

Between January 2006 and April 2010, 239 consecutive patients with COD and concomitant CAD referred to our hospitals were eligible for both CAS and PCI. The baseline clinical characteristics of all patients are reported in Table 1. Most patients were men, 76 patients (32%) had ACS, and 99 patients (41%) had multivessel CAD. Symptomatic COD was present in 49 (20.5%) patients. Procedure-related characteristics are shown in Table 2.

30-day outcomes. Table 3 details the occurrence of clinical events that comprised the primary and secondary endpoints. The primary endpoint of the study occurred in 4.2% (95% confidence interval [CI]: 2.02 to 7.56) of patients. The incidence of death, MI, and stroke was 0.4%, 1.3%, and 2.5%, respectively. One patient with symptomatic COD died 2 days after a simultaneous treatment of CAD and COD, after ventricular fibrillation due to a possible coronary stent thrombosis. Three nonfatal periprocedural MIs occurred in patients undergoing multivessel PCI within 30 days after successful CAS. Four patients with asymptomatic COD (1.7%) already treated by PCI had a major ipsilateral stroke after CAS: 3 patients within 6 h after the procedure and 1 patient 7 days after discharge. Two patients (0.8%) had a minor stroke a few hours after CAS.

The secondary endpoint after both procedures occurred in 20 patients (8.4%). In particular, TIA occurred in 6 patients (2.5%), major bleedings in 3 patients (1.3%), and acute kidney injury in 1 patient (0.4%). The results of the univariate analysis to test the relation between the

Table 1. Baseline Characteristics of the Patients (n = 239)

Age, yrs	73.13 ± 7.77
Age ≥80 yrs	52 (22)
Male	182 (76)
Hypertension	207 (87)
Diabetes	89 (37)
Hypercholesterolemia	181 (76)
Smoking	103 (43)
Family history of CAD	37 (15)
Chronic kidney disease*	30 (13)
Previous MI	51 (21)
Peripheral artery disease	25 (10.5)
LVEF	56.90 ± 6.36
Previous CABG	10 (4)
Previous PCI	18 (7.5)
ACS	76 (32)
Chronic stable angina	55 (23)
Extension of CAD	
1-vessel disease	140 (58)
2-vessel disease	59 (25)
3-vessel disease	40 (17)
Unprotected left main	8 (3)
Symptomatic COD	49 (20.5)
Previous stroke	6 (2.5)
Bilateral carotid stenosis >70%	42 (18)
Previous CEA	13 (5)
Previous CAS	7 (3)
Previous MI, stroke, or carotid/coronary revascularization	88 (37)
ACS or symptomatic COD	118 (49)
Dual APT	230 (96)
Statin use	180 (75)

Values are mean ± SD or n (%). *Defined as an estimated glomerular filtration rate of <60 ml/min per 1.73 m^2.

ACS = acute coronary syndrome(s); APT = antiplatelet therapy; CABG = coronary artery bypass graft; CAD = coronary artery disease; CAS = carotid artery stenting; CEA = carotid endarterectomy; COD = carotid obstructive disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2. Procedure-Related Characteristics

Staged procedures	201 (84)
Time between the staged procedures, days	23.6 ± 24.6
Simultaneous procedures	38 (16)
Sequence of the procedure: PCI first	192 (80)
PCI procedure success rate	235 (98)
Number of coronary stents implanted per patient	1.4 ± 0.3
Patients treated with ≥1 DES	148 (62)
CAS success rate	238 (99.6)
Cerebral protection device	
Filter wire	218 (92)
Proximal occlusion (Mo.Ma system, Invatec, Roncadelle, Italy)	20 (8)
Type of carotid stent	
Carotid Wallstent (Boston Scientific, Natick, Massachusetts)	116 (49)
AccuLink (Abbott Vascular, Santa Clara, California)	76 (32)
X-ACT (Abbott Vascular)	16 (7)
Precise (Cordis, Bridgewater, New Jersey)	22 (9)
Cristallo Ideale (Invatec)	8 (3)

Values are n (%) or mean ± SD.

DES = drug eluting stent(s); other abbreviations as in Table 1.

Table 3. Hierarchical Events at 30 Days From the Last Procedure

All deaths	1 (0.4)
Cardiac deaths	1 (0.4)
Neurological deaths	0 (0)
Other cause	0 (0)
Nonfatal MIs	3 (1.3)
All strokes	6 (2.5)
Major ipsilateral nonfatal strokes	4 (1.7)
Major contralateral nonfatal strokes	0 (0)
Minor strokes	2 (0.8)
MACCE (any death, MI, or stroke)	10 (4.2)
Transient ischemic attacks	6 (2.5)
Major bleedings	3 (1.3)
Acute kidney injury	1 (0.4)
Any of the above	20 (8.4)

Values are n (%).

MACCE = major cardiac and cerebrovascular event(s); MI = myocardial infarction.

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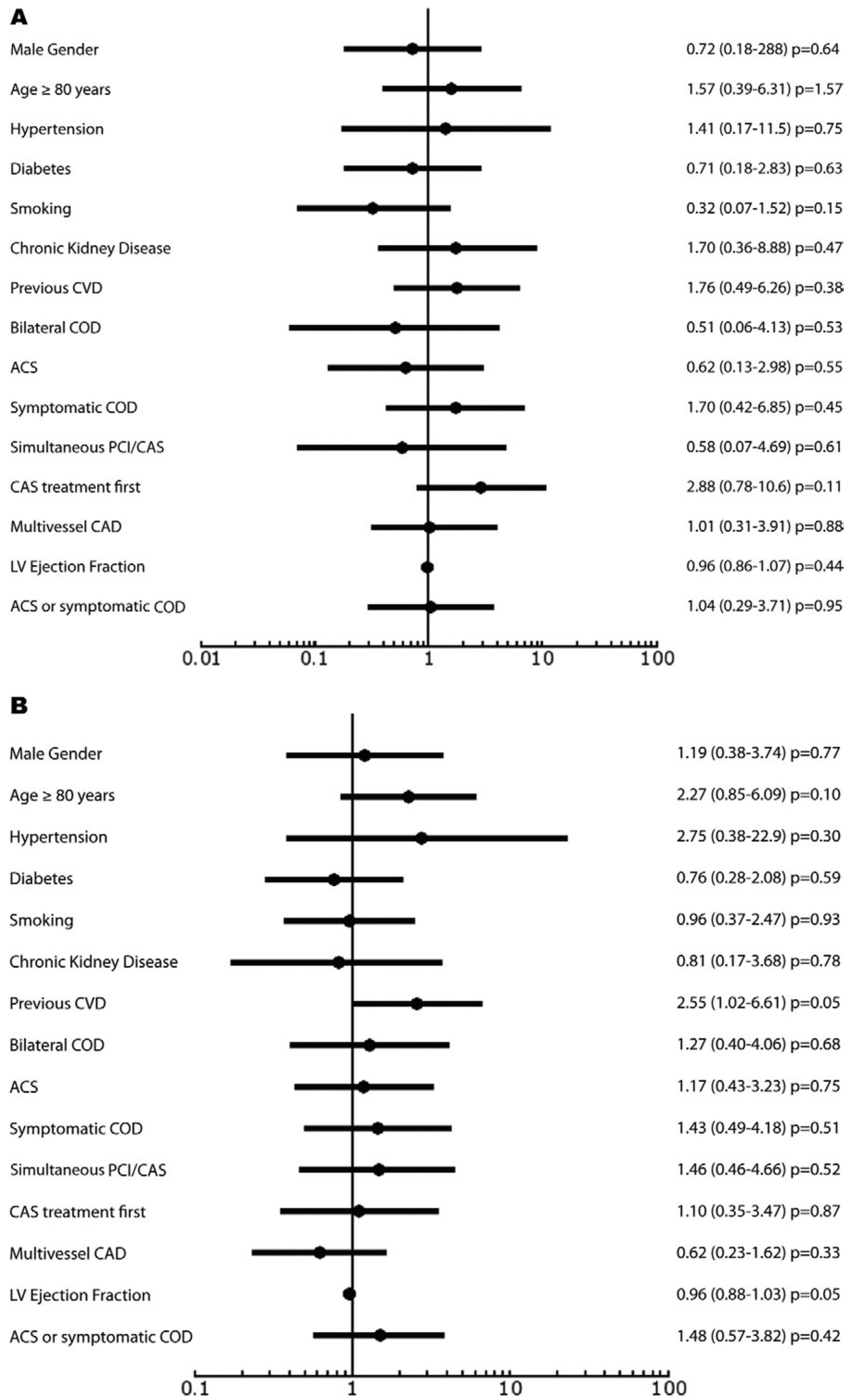

Figure 1. Univariate Linear Regression Analysis for the Occurrence of 30-Day Events Included in Primary and Secondary Endpoints

Univariate linear regression analysis for the occurrence of 30-day events included in primary **(A)** and secondary **(B)** endpoints. Numbers indicate the odds ratio (95% confidence interval) and the significance level (p) for each parameter. ACS = acute coronary syndrome(s); CAD = coronary artery disease; CAS = coronary artery stenting; COD = carotid obstructive disease; CVD = cardiovascular disease (including previous stroke, myocardial infarction, or carotid/coronary surgical or endovascular revascularization); LV = left ventricular; PCI = percutaneous coronary intervention.

clinical and treatment variables and the occurrence of events included in primary and secondary endpoints are shown in Figures 1A and 1B. Of note, the incidence of MACCE was not statistically different in patients treated with a simultaneous or staged approach (2.6% vs. 4.5%, p = 0.60), in patients treated by PCI first or by CAS first (3.1% vs. 8.5%, p = 0.10), in patients with symptomatic or asymptomatic COD (6.1% vs. 3.7%, p = 0.45), in patients older or younger than 80 years (5.8% vs. 3.7%, p = 0.52), in patients with ACS or chronic stable CAD (2.9% vs. 4.7%, p = 0.55), and in those with multivessel or single-vessel CAD (4.4% vs. 4.0%, p = 0.88).

The cumulative incidence of MACCE, TIA, major bleeding, and acute kidney injury was higher in patients with previous cardiovascular disease (previous MI, stroke, or carotid/coronary revascularization) than in patients with a first clinical episode (12.5% vs. 8.3%, p = 0.05) and, although not statistically significant, in patients older than 80 years (13.5% vs. 6.4%, p = 0.1).

Long-term follow-up. Median follow-up was 520 days (interquartile range: 416 to 812 days), with 204 of the patients (85.4%) being followed up for at least 1 year. The cumulative incidence of death, MI, and stroke was 4.2%, 2.1%, and 3.8%, respectively. The occurrence of MACCE after the first 30 days from the last procedure was 5.8% (Table 4). In particular, of 9 deaths (3.8%), 2 deaths (0.8%) were cardiac related, 1 (0.4%) was neurological, and 6 (2.5%) were of other causes. Two (0.8%) nonfatal MI and 3 strokes (1.2%) occurred: 2 (0.8%) major ipsilateral nonfatal strokes, and 1 (0.4%) minor stroke. Cumulative MACCE-free survival at 2 years was 82.3 ± 3.8% (SE). The Kaplan-Meier curve for 2-year freedom from death, all stroke, and MI is shown in Figure 2.

The results of the univariate analysis to test the relation between the clinical and treatment variables and the occurrence

Table 4. Hierarchical MACCE at 2-Year Follow-Up

Event	After 30 Days From the Last Procedure	All MACCE
All deaths	9 (3.8)	10 (4.2)
Cardiac deaths	2 (0.8)	3 (1.2)
Neurological deaths	1 (0.4)	1 (0.4)
Other cause	6 (2.5)	6 (2.5)
Nonfatal MIs	2 (0.8)	5 (2.1)
All strokes	3 (1.2)	9 (3.8)
Major ipsilateral nonfatal strokes	2 (0.8)	6 (2.5)
Major contralateral nonfatal strokes	0 (0)	0 (0)
Minor strokes	1 (0.4)	3 (1.2)
MACCE (any death, MI, or stroke)	14 (5.8)	24 (10.0)

Values are n (%). The second column refers to the events that occurred after 30 days from the last procedure, whereas the third column summarizes all MACCE from day 0 to long-term follow-up. Abbreviations as in Table 3.

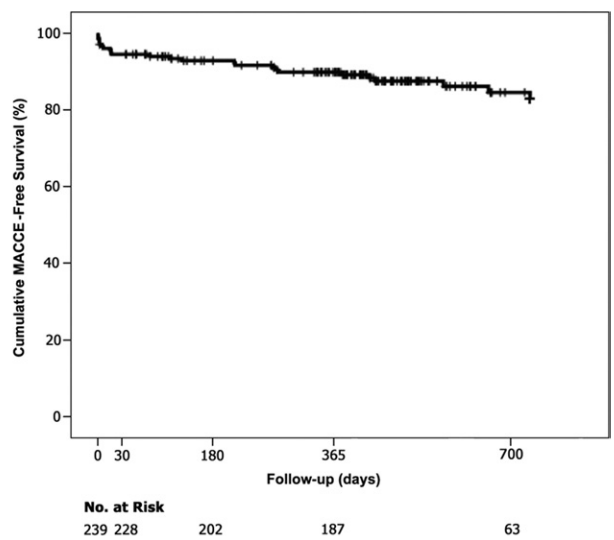

Figure 2. Kaplan-Meier Analysis for Cumulative Survival Free of MACCE at 2-Year Follow-Up

Estimated survival was of 82.3% ± 3.8% (SE). MACCE = major cardiac and cerebrovascular event(s).

of MACCE at long-term follow-up are shown in Figure 3. Patients with previous cardiovascular disease had significantly higher rates of MACCE than those with a first clinical episode (17.0% vs. 6.0%; hazard ratio: 3.34; 95% CI: 1.46 to 7.63, p = 0.004). The Kaplan-Meier curve for 2-year cumulative MACCE free survival in these 2 groups is shown in Figure 4.

Discussion

This prospective, multicenter study demonstrates that in patients with CAD and concomitant COD, a combined percutaneous revascularization treatment yields good immediate and long-term results.

Our research discloses the largest available series of its kind; it reinforces the concept of feasibility demonstrated in previous small series (20,21); and it compares favorably to similar populations treated by either totally surgical (5,12) or hybrid revascularization strategies (6,13,22–24). For instance, the 30-day rate of death/stroke/MI reported in a large meta-analysis of published studies on CAS plus CABG procedures was 9.4% (95% CI: 7.0 to 11.8) (6), which is about 2× the number of incidences reported in the present study.

Despite some obvious baseline differences when compared with series of patients needing CABG, it is worth noting that our results were obtained in a population of patients with several comorbidities, and who were treated with multiple coronary interventions in over 40% of cases. The high rate of freedom from death, stroke, or MI during the 2 years of follow-up supports the long-term efficacy of

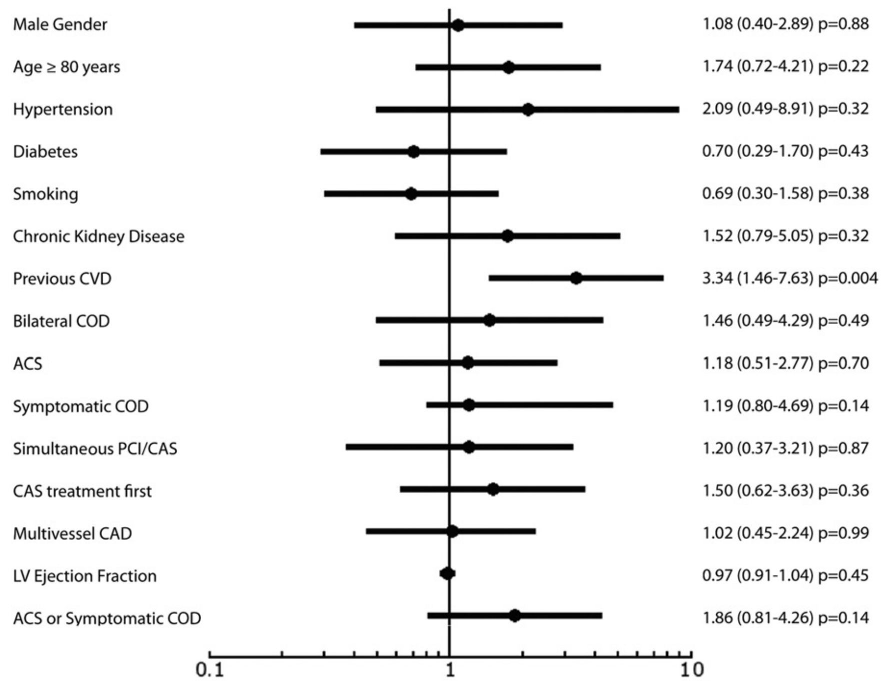

Figure 3. Univariate Cox Regression for the Occurrence of Major Cardiac and Cerebrovascular Events at Long-Term Follow-Up

Numbers indicate the hazard ratio (95% confidence interval) and the significance level (p) for each parameter. Abbreviations as in Figure 1.

this combined percutaneous strategy. Nonetheless, as expected, patients with more advanced cardiovascular disease, that is, those with previous stroke, MI, or carotid/coronary (surgical or percutaneous) revascularization, exhibited worse short- and long-term outcomes. Indeed, according to recent findings (9), elderly patients exhibited a higher incidence of adverse events at 30 days, although this difference did not reach a statistical significance, probably due to the relatively small sample size of our series.

Notably, the low incidence of periprocedural complications is likely to be also related to the experience developed in dedicated centers and might not be easily and immediately replicable outside similar contexts. Indeed, the FRIENDS Study Group is committed to vascular care, according to well-defined standards by which all patients are evaluated by a cardiovascular team after diagnostic coronary and cervical-cerebral angiography according to a "case-tailored" approach (17). In all CAS procedures, materials, devices, and techniques were matched to specific lesions or anatomies. Among patients with multivessel CAD, physicians pursued the most complete degree of revascularization and optimal stent implantation. The sequence of the procedures and the strategy (staged or simultaneous) were established by the cardiovascular team on an individual patient basis. Finally, the optimal medical treatment on top of interventions, as well as a tight clinical follow-up focused on secondary prevention was achieved in almost all patients. All these factors play an important role on the long-term outcome of vascular interventions and may have influenced our results.

Therefore, compared with previous experiences with surgical or hybrid revascularization strategies, this combined percutaneous approach offers the following advantages. 1) Its less invasive nature may prove particularly appropriate for complex patients (i.e., those with more advanced cardiovascular disease), who are suited for percutaneous treatment. 2) The sequence of the 2 procedures is easier to plan, and in most cases, coronary revascularization can be safely performed first (unless otherwise recommended, as in patients with severe symptomatic COD), without an increased risk of stroke. Indeed, evidence in support of coronary revascularization in patients needing carotid interventions is becoming more consistent (25), although it remains to be proved in large randomized clinical trials. 3) The shorter hospital stay might translate into a reduction in costs compared with the costs of hybrid or surgical strategies.

Study limitations. First, the results of this study, performed at high-volume centers, may not be extrapolated to less experienced centers. Second, due to the relatively small sample size, the low rate of events and the presence of only 1 independent predictor of MACCE at univariate analysis, the multivariable analysis has not been reported. Third, the lack of systematic performance of diffusion-weighted magnetic

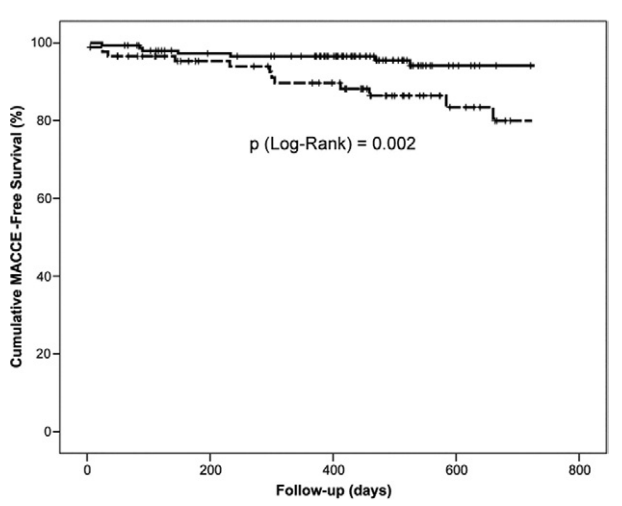

Figure 4. Kaplan-Meier Analysis for Cumulative Survival Free of MACCE at 2-Year Follow-Up in Patients With or Without Previous Stroke, MI, or Carotid/Coronary Revascularization

Kaplan-Meier analysis for cumulative survival free of major cardiac and cerebrovascular events (MACCE) at 2-year follow-up in patients with **(dashed line)** or without **(solid line)** previous stroke, myocardial infarction (MI), or carotid/coronary revascularization. Survival in these 2 groups was significantly different according to the log-rank test (67.3 ± 8.3% vs. 90.1 ± 3.5%; p = 0.002).

resonance imaging might underestimate the incidence of clinically silent cerebral infarction after CAS (26). Fourth, given its nonrandomized nature, our results cannot be compared with clinical trials on CEA and CABG.

Conclusions

In patients with COD and concomitant CAD, a combined percutaneous treatment performed in high-volume centers skilled for vascular care yields good immediate and long-term results. Thus, it may be a valuable alternative to the entirely surgical or hybrid approaches. Further studies are warranted to confirm the safety and durability of this combined percutaneous approach.

Reprint requests and correspondence: Dr. Fabrizio Tomai, Department of Cardiovascular Sciences, Division of Cardiology, European Hospital, Via Portuense 700, 00149 Rome, Italy. E-mail: f.tomai@tiscali.it.

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